

REMARKS

The Response filed in response to the Office Action mailed September 2, 2010 is believed to address each and every issues contained in the Office Action. Favorable reconsideration and allowance of the application are respectfully requested.

Status of the Claims

Claims 1-13 are pending in the application, from which claims 11-13 have been withdrawn from consideration.

Claims 1-10 are under consideration and stand rejected.

No claims are amended, added, or canceled.

Withdrawn Rejection

Applicant thank the Examiner for withdrawing the rejection under 35 USC 112, first paragraph in light of Applicant's amendment filed July 2, 2010.

Response to Claim Rejections under 35 USC § 103

1. Summary of Rejections

In the Office Action, claims 1-9 are rejected under 35 U.S.C. 103(a) as assertedly being unpatentable over Patel et al. (US Pre-Grant Publication 2003/0064097) in combination with Kawamura et al. (US Pre-Grant Publication 2004/0219208).

In the Office Action, claim 10 is rejected under 35 U.S.C. 103(a) as assertedly being unpatentable over the combined teachings of Patel et al. and Kawamura et al. as set forth above with respect to claim 1 in combination with Nielsen et al. (USPN 5,716,558).

Patel, Kawamura and Nielsen were previously cited and discussed in the earlier Office Actions and previously filed Amendments. Therefore, the details thereof are not repeated herein, for the brevity.

In brief, the Examiner recognizes that Patel et al. do not expressly teach removal (e.g., displacement) of the mixed organic solvent portion of the dispersing medium by washing the coated particles with additional supercritical fluid. Office Action, page 5, second full paragraph.

The Examiner also recognizes that Patel et al. do not teach the claimed order of the addition of components of the instantly claimed method. Office Action, page 7, lines 10-11.

Furthermore, the Examiner admits that neither of Patel et al., nor Kawamura et al. teach polymer/active weight ratio, percent range of the hydrophilic polymer or the weight ratio of the two organic solvents mixed, as claimed by Applicants. Office Action, page 7, lines 19-21.

The Examiner contends that the selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results. With regard to the specific range of the polymer/active weight ratio and the percent range of the hydrophilic polymer or the weight ratio of the two organic solvents mixed, as recited in the claims of the instant application, the Examiner asserts that the amounts and ratios of specific ingredients in a composition are a result effective parameter that a person of ordinary skill in the art would routinely optimize as is format of oral dosage. The Examiner concludes that, absent some demonstration of unexpected

results from the claimed parameters, the alleged optimization of ingredient amounts would have been obvious at the time of Applicant's invention. Office Action, page 8, lines 5-7.

Nielsen et al. is cited as teaching methods for spraying liquid compositions by using compressed fluids such as carbon dioxide, to form solid particulates and coating powders which may be produced with narrow particle size distributions.

With regard to the Applicant's arguments for unexpectedly superior results of the claimed subject matter, in comparison with the results of Examples 2 and 3 in Patel et al., the Examiner contends that such a comparison is not commensurate in scope with the instant invention as the active ingredients each will have distinct solubilities.

2. Applicant's Responses

Applicant respectfully traverses for the following reasons.

2-1. The combined teachings of Patel, Kawamura, and Nielsen fail to teach all and every limitations of independent claim.

The combined teachings of Patel, Kawamura, and Nielsen fail to the recitation "spraying the *solution mixture of Step 1) to a supercritical fluid to form crystallized particles* of the mixture of paclitaxel and the pharmaceutically acceptable additive, the crystallized particles containing *paclitaxel of an altered crystallinity.*"

2-2. No guidance or motivation to modify the defective combined teachings of the cited references to reach the claimed invention with reasonable expectation of success.

As recognized by the Examiner, the combined teachings of Patel and Kawamura, in view of Niesen do not teach certain features of the claimed method.

Even thought the Examiner asserts that the selection of certain order of the recited steps and the specified ratios and other conditions are subject to optimization, Applicant respectfully, but strongly disagrees.

None of Patel, Kawamura, and Nielsen disclose or suggest that, when using supercritical fluid method among numerous methods for preparing a solid dispersion, the solubility of paclitaxel among such a large number of drugs can be remarkably improved by the change of crystallinity of paclitaxel.

Even if the cited references are combined together, a person skilled in the art would not have been able to select paclitaxel and supercritical fluid method and conceive the unique process for the improvement of paclitaxel solid dispersion of the subject invention.

2-3. Claimed invention shows unexpectedly remarkable effects

Moreover, the effects stemming from the unique combination of paclitaxel and a supercritical fluid are recognized as unexpectedly remarkable compared with those of the cited reference.

As previously discussed in Amendment of July 10, 2010, the solubilities of paclitaxel solid dispersions prepared by the supercritical fluid process of the **subject invention** are remarkably **higher (about 3,000 times)** than that of the solid dispersion prepared by using liquid carbon dioxide or a conventional paclitaxel powder (see Table 25 of the subject specification). On the contrary, in **Patel**, the dissolution ratios of the glyburide composition in Example 2 and the progestetone composition in Example 3 of Patel show **merely 2 and 3 times higher** than that of the pure bulk drug (see Figures 1, 2A and 2B of Patel). Furthermore, the amounts of surfactants (e.g., Myrj 52) comprised in the composition for further improving solubility of the

subject invention, i.e., 2.5 to 25g, is much lower than those employed in Examples 2 to 5, and 13 to 28 of Patel.

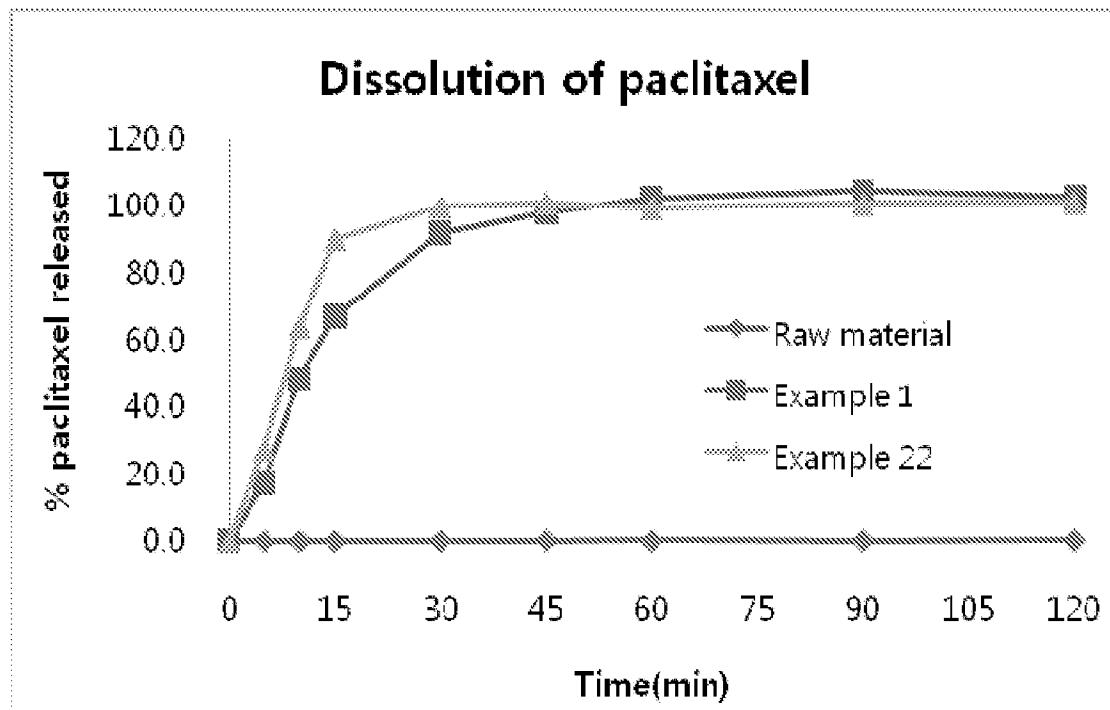
It is noted that the Examiner contends that the above comparison is not commensurate in scope with the instant invention as the active ingredients each will have distinct solubilities. Applicant respectfully disagrees. While it is noted that the solubility comparison was made for a different drug, the difference in 3,000 times higher vs. 2-3 times higher is sufficient to show unexpectedly superior effects of the claimed method.

Nevertheless, solely for the Applicant's interests to advance the prosecution, Applicant conducted additional experiments (dissolution tests) for the paclitaxel solid dispersions prepared by the process explained in Examples 1 and 22 as well as pure bulk paclitaxel (raw material) as a control, and obtained the following results.

Dissolution Test Conditions:

- i. Apparatus : USP dissolution type 2
- ii. Material : Pure bulk paclitaxel (Raw material), paclitaxel solid dispersions obtained in Example 1 and Example 22 of the instant application (100 mg as paclitaxel)
- iii. Medium : distilled water, 900mL, 37±0.5°C
- iv. Speed : 100rpm

The results are shown in the graph below.



The above results shows that, when the test materials were subjected to dissolution tests under the above-listed conditions, the solid dispersions of Examples 1 and 22 of the instant application showed almost 100% release within about 1 hour and a maximum dissolution of 2,500 $\mu\text{g}/\text{ml}$. To the contrary, the pure bulk paclitaxel showed a maximum 0.3% release ($\leq 1\mu\text{g}/\text{ml}$), which indicates that paclitaxel, which is sparingly soluble in an aqueous medium such as water, is not released from the formulation without an aid of a surfactant. Similarly, when another sparingly soluble drug, tacrolimus was tested, solid dispersions of tacrolimus obtained by the claimed method showed 2,500 $\mu\text{g}/\text{ml}$ dissolution. Tacrolimus is reported to have 3 $\mu\text{g}/\text{ml}$ dissolution.

With regard to glyburide, which was tested in Patel, is reported to have about 4 μ g/ml release rate. Patel reports that its formulation of glyburide showed 2-3 times higher than the pure bulk glyburide, according to the results shown in FIG. 1.

Accordingly, Applicant respectfully submits that the above data sufficiently show the unexpectedly superior effects of the claimed method and claims 1-10 of the instant application are patentable over the combination of Patel, Kawamura, and Nielsen.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number **202-775-7588**.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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